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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,995	04/16/2004	Niels Christian Kaarsholm	6573.204-US	9239

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EXAMINER	
BRADLEY, CHRISTINA	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
03/18/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/825,995	KAARSHOLM ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,128-135,142-170 and 205-218* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 128-135, 142-170 and 205-218* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/14/2008 has been entered. Claims 1, 128-135, 142-170 and 205-218 are pending.

Claim Objections

2. Claims 1, 166-170 and 205-218 are objected to because of the following informalities: in claim 1, line 11, the word "is" appears twice following "M"; in claim 1, the variable R^{50B} is defined but does not appear in the claimed formula; in claim 1, lines 15-18 and on the top of page 3, multiple spaces separate the recited chemical groups; and in claim 1, the colon following the phrase "T is" is inconsistent with the structure of the rest of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 128-135 and 142-165 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 128-135 and 142-165 depend on cancelled claims.

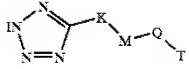
5. Claims 1, 166-170 and 205-218 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: a definition for the variable I in the formula recited in claim 1.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 166-170 and 205-218 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

8. The claims are drawn to a pharmaceutical composition comprising insulin and a zinc-binding ligand which reversibly binds to a $His^{B10}Zn^{2+}$ site of an insulin hexamer, wherein the ligand is



wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, -C_1-C_6-alkyl-S-, -C_1-C_6-alkyl-O-, -C(=O)-, or -C(=O)-NH-, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38},

U is a valence bond, C_1-C_6-alkenylene, -C_1-C_6-alkyl-O- or C_1-C_6-alkylene wherein any C_1-C_6-alkyl moiety is optionally substituted with C_1-C_6-alkyl,

R^{38} is C_1-C_6-alkyl, aryl, wherein the alkyl or aryl moieties are optionally substituted with one or more substituents independently selected from R^{39},

R^{39} is independently selected from halogen, cyano, nitro, amino,

M is indolylene optionally substituted with one or more substituents independently selected from R^{40},

R^{40} is selected from hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{41}, -$NR^{41}R^{42}$, -SR^{41}, -$NR^{41}S(O)_2R^{42}$, -$S(O)_2NR^{41}R^{42}$, -$S(O)NR^{41}R^{42}$, -$S(O)R^{41}$, -$S(O)_2R^{41}$, -$OS(O)_2R^{41}$, -$C(O)NR^{41}R^{42}$, -$OC(O)NR^{41}R^{42}$, -$NR^{41}C(O)R^{42}$, -$CH_2C(O)NR^{41}R^{42}$, -OC_1-C_6-alkyl-$C(O)NR^{41}R^{42}$, -CH_2OR^{41}, -$CH_2OC(O)R^{41}$, -$CH_2NR^{41}R^{42}$, -$OC(O)R^{41}$, -OC_1-C_6-alkyl-$C(O)OR^{41}$, -OC_1-C_6-alkyl-OR^{41}, -S-C_1-C_6-alkyl-$C(O)OR^{41}$, -C_2-C_6-alkenyl-$C(=O)OR^{41}$, -NR^{41}-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{41}$, -NR^{41}-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{41}$- , -$C(O)OR^{41}$, -C_2-C_6-alkenyl-$C(=O)R^{41}$, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)-O-C_1-C_6-alkyl; C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{43}; aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44},

R^{41} and R^{42} are independently selected from hydrogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkenyl, aryl-C_1-C_6-alkyl or aryl, wherein the alkyl moieties may optionally be substituted with one or more substituents independently selected from R^{45}, and the aryl moieties may optionally be substituted with one or more substituents independently selected from R^{46};

R^{41} and R^{42} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{43} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{41}$, and $-NR^{41}R^{42}$

R^{44} is independently selected from halogen, $-C(O)OR^{41}$, $-CH_2C(O)OR^{41}$, $-CH_2OR^{41}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$ and C_1-C_6-alkyl,

R^{45} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, -O-C_1-C_6-alkyl, -C(O)-O-C_1-C_6-alkyl-, -COOH and $-NH_2$,

R^{46} is independently selected from halogen, $-C(O)OC_1$-C_6-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, -OH, $-OC_1$-C_6-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl,

Q is a valence bond, C_1-C_6-alkylene, -C_1-C_6-alkyl-O-, -C_1-C_6-alkyl-NH-, -NH-C_1-C_6-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C_1-C_6-alkyl, -C(=O)-, or -C_1-C_6-alkyl-C(=O)-N(R^{47})- wherein the alkyl

moieties are optionally substituted with one or more substituents independently selected from R^{48},

R^{47} and R^{48} are independently selected from hydrogen, C_1-C_6-alkyl, aryl optionally substituted with one or more R^{49},

R^{49} is independently selected from halogen and -COOH,

T is hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkyloxy-carbonyl, wherein the alkyl, alkenyl and alkynyl moieties are optionally substituted with one or more substituents independently selected from R^{50}; aryl, aryloxy, aryloxy-carbonyl, aryl-C_1-C_6-alkyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkyny-, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl, heteroaryl-C_2-C_6-alkynyl, wherein any alkyl, alkenyl , alkynyl, aryl and heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{50},

R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy, -C(=O)-NH-C_1-C_6-alkyl-aryl, -C(=O)- R^{50A}-C_1-C_6-alkyl, -C(=O)-NH-$(CH_2CH_2O)_m$$C_1$-$C_6$-alkyl-COOH,

heteroaryl, heteroaryl-C_1-C_6-alkoxy, -C_1-C_6-alkyl-COOH, -O-C_1-C_6-alkyl-COOH,

-$S(O)_2R^{51}$, -C_2-C_6-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, =O, -$N(R^{51}R^{52})$, wherein m is 1, 2, 3 or 4, and wherein the aryl or heteroaryl moieties are optionally substituted with one or more R^{53},

R^{50A} and R^{50B} are independently selected from -C(O)OC_1-C_6-alkyl, -COOH, -C_1-C_6-alkyl-C(O)OC_1-C_6-alkyl, -C_1-C_6-alkyl-COOH, or C_1-C_6-alkyl,

R^{51} and R^{52} are independently selected from hydrogen and C_1-C_6-alkyl,

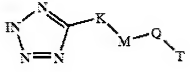
R^{53} is independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, -C_1-C_6-alkyl-COOH, -C_2-C_6-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, or -$N(R^{51}R^{52})$,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

9. The specification discloses the complete structure of numerous species of the genus defined by the formula above (hereafter formula I). Beginning with paragraph 2421, the specification presents general procedures and specific examples for the preparation of compounds of this genus. In each of the examples, M is always an unsubstituted indolylene. In each of the examples, K is always a valence bond and the tetrazole ring is always attached to position 5 of the indolylene ring, with the exception of example 811 wherein it is attached at position 4. In the examples that follow only three options are presented for Q: a valence bond (example 810), CH_2 (examples 806-809, 811-864), and C=O (examples 865-872, 986-991 and 1001-1009). In the examples that follow, only four options are presented for T: H (example 810), phenyl (806, 807, 812-824, 826-833, 835-843, 845, 847-859, 865-870, 872, 986-990 and 1001-1009), naphthyl (825, 846, 871 and 991) and biphenyl (809, 834, 844, and 860-864), wherein the rings are substituted at a single position with halogen, COOH, CF_3, OCH_3, CH_3, isopropyl, CN, NO_2, NH_2 or OCF_3, or substituted at two positions with halogen, OCH_3 or CF_3. Collectively, these examples represented a well-defined subgenus of formula I that is fully supported in the specification. The specification fails to disclose a single species outside this subgenus of formula I. In addition, the specification does not disclose the chemical/physical properties of any additional species or guidance on how to obtain specific compounds with the claimed functional properties of reversibly binding to a $His^{B10}Zn^{2+}$ site of an insulin hexamer. Accordingly, in the

absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the full scope of the claimed genus.

10. With the exception of compounds in the subgenus described above, the skilled artisan cannot envision the detailed chemical structure of the claimed zinc ligands. Therefore, only compounds with the following structural properties, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. §112, first paragraph:



I is H;

K is a valence bond;

M is an unsubstituted indolylene;

Q is a valence bond, CH_2, or C=O;

T is H, phenyl, naphthyl or biphenyl,

wherein the phenyl, naphthyl or biphenyl may be optionally substituted at a single position with halogen, COOH, CF_3, OCH_3, CH_3, isopropyl, CN, NO_2, NH_2 or OCF_3, or optionally substituted at two positions with a moiety independently selected from halogen, OCH_3 or CF_3; and

the tetrazole ring is always attached to position 4 or 5 of the indolylene.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. The rejection of claims 1, 205 and 213-218 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunn (U.S. Patent No. 5,830,999) in view of Franke & Groeneveld (*Transit. Met. Chem.*, **1981**, *6*, 54-6) is withdrawn in light of the fact that claim 1 has been amended to include the limitations of claims 127 and 141 (presently cancelled).

13. The rejection of claims 1, 127-140, 150-153, 155-157, 205 and 213-218 under 35 U.S.C. 103(a) as being unpatentable over Dunn (U.S. Patent No. 5,830,999) in view of Franke & Groeneveld (*Transit. Met. Chem.*, **1981**, *6*, 54-6) and Ciarkowski *et al.* (*Org. Mag. Res.*, **1979**, *12*, 631-6) is withdrawn in light of the fact that claim 1 has been amended to include the limitations of claims 127 and 141 (presently cancelled).

14. The rejection of claims 1, 127-140, 150-153, 155-157, 205 and 213-218 under 35 U.S.C. 103(a) as being unpatentable over Dunn (U.S. Patent No. 5,830,999) in view of Franke & Groeneveld (*Transit. Met. Chem.*, **1981**, *6*, 54-6) and Makovec *et al.* (*J. Med. Chem.*, **1992**, *35*, 3633-40) is withdrawn in light of the fact that claim 1 has been amended to include the limitations of claims 127 and 141 (presently cancelled).

15. The rejection of claims 1, 127-170, and 205-218 under 35 U.S.C. 103(a) as being unpatentable over Dunn (U.S. Patent No. 5,830,999) in view of Olsen *et al.* (US 2003/0229120)

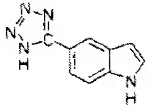
is withdrawn. Applicant has provided evidence in this file showing that the invention was owned by, or subject to an obligation of assignment to, the same entity as Olsen *et al.* at the time this invention was made.

16. Claims 1 and 205-218 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunn (U.S. Patent No. 5,830,999) in view of Franke & Groeneveld (*Transit. Met. Chem.*, **1981**, *6*, 54-6), Wentrup *et al.* (*J. Am. Chem. Soc.*, **1984**, *106*, 3705-6) and Havelund *et al.* (WO 95/07931).

17. Dunn teaches that ligands that bind tightly and specifically to the two His^{B10} –bound Zn^{2+} ions in insulin stabilize formulations of insulin hexamers for pharmaceutical use (column 3, lines 57-61). Regarding claim 205, Dunn teaches compositions of fast acting insulin (column 7, line 7). Regarding claims 213-216, Dunn teaches compositions of at least 2 moles of zinc per mole of insulin (column 7, line 19) and at least 22 moles of phenolic compound per insulin hexamer (column 6, line 60). Regarding claims 217 and 218, Dunn teaches compositions with isotonicity agents and buffers (column, 7, line 11). Dunn does not teach the tetrazole zinc ligands of the claimed invention.

18. Franke & Groeneveld teach that tetrazoles can coordinate zinc (abstract).

19. Wentrup *et al.* teach the following tetrazole compound:



wherein with respect to the formula in claim 1, K is a valence bond, M is an unsubstituted inolylene, Q is a bond and T is hydrogen (Scheme II, compound 11).

20. Havelund *et al.* teach protracted human insulin derivatives including B29-N^{ε}-myristol-des(B30) human insulin (Tables 1 and 2, Example 18).

21. It would have been obvious to one of ordinary skill in the art to substitute the tetrazole compound of Wentrup *et al.* for the zinc ligands in the insulin hexamers taught by Dunn. The skilled artisan would have been motivated to do so because Dunn teaches that ligands for the two His^{B10} –bound Zn^{2+} ions in insulin stabilize insulin hexamers for pharmaceutical use (column 3, lines 57-61) and because Franke & Groeneveld teach that tetrazole containing compounds can be used as a zinc ligand (abstract). There would have been a reasonable expectation of success given that the tetrazole compound of Wentrup *et al.* is functionally equivalent to the ligands of Dunn based on their ability to coordinate zinc. The skilled artisan would have been further motivated to use the insulin derivative B29-N^{ε}-myristol-des(B30) human insulin taught by Havelund *et al.* because it exhibits the highest index of protraction as compared to other protracted derivatives taught by Havelund *et al.* Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

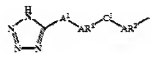
ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. Claims 1, 166-170 and 205-218 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 11/226,870. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 166-170 and 205-218 are generic to all that is recited in claims 37 and 38 of copending Application No. 11/226,870. That is claims 37 and 38 of copending Application No. 11/226,870 fall entirely within the scope of claims 1, 166-170 and 205-218 or, in other words, claims 1, 166-170 and 205-218 are anticipated by claims 37 and 38 of copending Application No. 11/226,870. Specifically, claims 37 and 38 of copending Application No. 11/226,870 recite pharmaceutical compositions comprising insulin and a ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R state insulin hexamer wherein the ligand has the formula identical to that in claim 1 of the instant application. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

23. The rejection of claims 1, 127-170, 205 and 213-218 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over copending Application No. 10/332,541 in view of Dunn (U.S. Patent No. 5,830,999) is withdrawn because claims drawn to compositions of insulin and the claimed zinc ligands are withdrawn in copending Application No. 10/332,541 for pertaining to a non-elected invention.

24. Claims 1, 127-170, 205 and 213-218 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18 and 19 of copending Application No. 11/227,760 in view of Dunn (U.S. Patent No. 5,830,999). The claims of the copending application are drawn to compounds of formula CGr-Lnk-Frg1-Frg2-X wherein CGr is a chemical group which reversibly binds to a His^{B10} Zn^{2+} site of an insulin hexamer and includes compounds of the structure



wherein the variables are defined above (the '760 application uses the variables K, M, Q and T instead of A^1, AR^1, C^1, and AR^2 but the genus is equivalent and for simplicity will not be repeated here). Dunn teaches that ligands that bind tightly and specifically to the two His^{B10} Zn^{2+} sites in insulin stabilize formulations of insulin hexamers for pharmaceutical use (abstract). It would have been obvious to one of ordinary skill in the art to combine the CGr ligands of copending application 11/227,760 with the insulin hexamers in the absence of the Lnk-Frg1-Frg2-X moiety. The skilled artisan would have been motivated to do so given that Dunn teaches that ligands for the His^{B10} Zn^{2+} sites stabilize the hexamer form of insulin and the claims of copending Application No. 11/227,760 teach that the CGr groups bind to the His^{B10} Zn^{2+} sites. There would have been a reasonable expectation of success given that the CGr compounds are functionally equivalent to the ligands of Dunn. This is a provisional obviousness-type double patenting rejection.

25. Because Applicant has not presented arguments against these rejections, they are maintained.

Conclusion

26. No claims are allowed.
27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday, Tuesday and Thursday, 8 A.M. to 5:30 P.M.
28. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
29. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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